Allergy represents a significant and increasing health problem worldwide. Allergic symptoms have a negative impact on patients' lives and societal economy. Allergy immunotherapy should be included in optimal treatment strategies.

Allergy immunotherapy: the future of allergy treatment

Jørgen Nedergaard Larsen , Louise Broge and Henrik Jacobi

ALK A/S, Bøge Allé 1, DK-2970 Hørsholm, Denmark

Allergic respiratory disease represents a significant and expanding health problem worldwide. Allergic symptoms, such as asthma and hay fever, cause sleep impairment and reduce school and work performance. The cost to society is substantial. Allergen avoidance and pharmacotherapy cannot control the disease. Only allergy immunotherapy has disease-modifying potential and should be included in optimal treatment strategies. Allergy immunotherapy was first administered as subcutaneous injections and has been practiced for the past 100 years or so. Recently, tablet-based sublingual allergy immunotherapy (SLIT) was introduced with comprehensive clinical documentation. SLIT tablets represent a more patient-friendly concept because they can be used for self-treatment at home.

Introduction

Respiratory allergic disease represents a significant health problem in both developed and developing countries [1]. During the past four decades, a dramatic increase in the prevalence of allergic disease has occurred, and respiratory allergic disease is now the most common chronic disease among adolescents and young adults [2,3]. The increase is especially problematic in children because of the prognosis of chronic and frequently aggravating disease [4].

The clinical manifestations of allergic disease include: asthma; rhinitis; conjunctivitis; anaphylaxis; drug-, food-, and insect allergy; eczema; urticaria (hives); and angioedema. Respiratory manifestations are the most prevalent, affecting up to 30% of the general population [4]. According to statistics from the World Health Organization (WHO), hundreds of millions of people in the world have rhinitis and it is estimated that 235 million people have asthma (http://www.who.int/mediacentre/factsheets/fs307/en/index.html). Asthma is a chronic inflammatory disorder of the airways associated with airway hyper-responsiveness and airflow obstruction (http://www.ginasthma.org/). Allergic rhinitis implies a blocked or runny nose, sneezing, and itching secondary to immunoglobulin (Ig)-E-mediated inflammation of the nasal mucosa [5]. Rhinitis often occurs in combination with conjunctivitis, an inflammatory disease of the eye characterized by flushing, swelling, itching, and watering of the eyes. Asthma and rhinoconjunctivitis are linked by epidemiological, physiological, and pathological characteristics. The

Jørgen Nedergaard Larsen received a MSc in biochemistry from the University of Copenhagen in 1985 and a PhD in molecular biology from the University of Copenhagen in 1991. He was among the first to study recombinant allergens and was working in the research team behind the first 3D structure of an important inhalation allergen, the birch pollen major allergen, published in 1996. Jørgen has been on international committees relating to allergen nomenclature, and allergen standardization and immunotherapy. He is a co-author of 37 original articles and 27 reviews and book chapters. Jørgen is currently a senior scientific communication manager with ALK.

Louise Broge received a MSc in inorganic chemistry from the University of Copenhagen in 1997 and a PhD in bioinorganic chemistry from the Royal Veterinary and Agricultural University in 2003. After a period in academia studying model systems of metalloenzymes and teaching general and physical chemistry, Louise was employed by ALK in 2007, where she has been involved in the clinical development of SLIT tablets for several allergen species, in particular the pediatric programs. She is currently a senior medical writer with ALK.

Henrik Jacobi qualified with a degree in medicine from the University of Copenhagen in 1993. In 1995, he took up a research position at the Allergy Clinic and the Laboratory of Medicinal Allergology at the National University Hospital in Copenhagen, Denmark, where he did clinical as well as experimental research. Henrik joined ALK in 2000 as a senior scientist in the research department. In 2001, Henrik was promoted to be head of this department and, in 2003, he was appointed executive vice president for research and development at ALK. Henrik is the co-author of several text-book chapters and 22 original articles on allergy and immunology.

Corresponding author: Larsen, J.N. (jnldk@alk.net)

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GLOSSARY

Allergen a molecule that is foreign to the human body and capable of inducing an immune response in humans, characterized by the presence of allergen-specific IgE antibodies.
Allergy immunotherapy the administration of allergen (i.e., epitopes) for the purpose of inducing allergen-specific immunological tolerance to treat allergic disease. It is a joint designation covering allergen and nonallergen immunotherapy [94].
Epitope an integral part of a molecule capable of interaction with specific receptors, IgE antibodies, or T cell receptors, of the adapted immune response.
Pharmacotherapy the administration of a chemically synthesized pharmaceutical product to treat allergic disease. It is symptom-relieving therapy without the induction of allergen-specific tolerance.
SCIT subcutaneous immunotherapy [94].
Sensitization priming of the immune system that also involves the generation of immunological memory. It is antigen specific and essentially irreversible. B and T cells proliferate and generate antigen-specific IgE antibodies and T cells. Sensitization is the first step in the development of allergy.
SLIT sublingual immunotherapy [94].
SLIT-drop sublingual immunotherapy using a liquid formulation.
SLIT-tablet sublingual immunotherapy using a solid formulation.
Subcutaneous under the skin. Vaccines are often delivered by hypodermic injection into the subcutaneous tissue located immediately beneath the skin.
Sublingual under the tongue. Medicine can be administered sublingually on the mucosal surface in the hollow under the tongue.

genetic predisposition to develop IgE-mediated sensitivity to common aeroallergens is the strongest predicting factor for the development of rhinoconjunctivitis as well as asthma [1].

It is becoming increasingly clear that allergy is a systemic immunological disease initiated by the priming of an adaptive immune response to common allergens (see Glossary) [6] (Fig. 1). Regardless of the affected organ, allergic respiratory disease is characterized by the presence of allergen-specific IgE antibodies and eosinophilic inflammation. The allergic reaction is biphasic, with an immediate reaction occurring within minutes following allergen exposure and a late-phase reaction occurring hours later [6]. The immediate reaction is caused by release of preformed mediators from basophils and mast cells upon cross-linking of IgE bound to high-affinity receptors on the cell surface. The late-phase allergic reaction is caused by mobilization and attraction of inflammatory cells, such as eosinophils, basophils, neutrophils, and mononuclear cells [6].

Current clinical guidelines recommend a combination of patient education, allergen avoidance, pharmacotherapy, and allergy immunotherapy for treatment [5]. Allergen avoidance is indicated whenever feasible, although, in practice, adequate symptom control is difficult to achieve with allergen avoidance alone. Although safe and inexpensive drugs are available for the treatment of allergic symptoms, many patients report insufficient symptom control. Importantly, pharmacotherapy has no effect on the progression of the disease and treatment has to be administered repeatedly as long as symptoms prevail, which often means life-long.

Allergy immunotherapy is a causal treatment targeting the underlying allergic disease, affecting basic immunological mechanisms and resulting in the induction of immunological tolerance [7]. Induced tolerance implies disease modification, the clinical effects of which are sustained symptom relief after completed treatment and/or prevention of disease progression. The latter includes impeded aggravation of existing symptoms, preventing the development of asthma in children with allergic rhinoconjunctivitis and, potentially, also preventing supervening new allergies.

The capacity to alter the natural course of the disease differentiates allergy immunotherapy from other treatment modalities. Therefore, spending time, effort, and money on immunotherapy represents an investment that will return sustained benefits from improved prognosis and a relieved burden of disease. The clinical effects during ongoing treatment are firmly established; the future aim for allergy immunotherapy is to expand the evidence base concerning the benefits of disease modification. Here, we provide an update within the area of allergy immunotherapy, with particular focus on current state-of-the-art and the evidence base already established.

Allergic disease

Allergy is a widespread disease with increasing prevalence

The prevalence of allergic disease is increasing [3]. At the beginning of the 20th century, allergy was viewed as a rare disease. Today, the most common manifestation of allergic disease is rhinoconjunctivitis, affecting some 45% of young adults in selected countries [3]. In Europe, a large study based on telephone interviews among the general population reported prevalences of allergic rhinoconjunctivitis of between 17% in Italy and 29% in Belgium, with an overall average of 23% [8], in good agreement with results from the European Community Respiratory Health Survey [9]. The European Academy of Allergy and Clinical Immunology predicts that, within the next few decades, more than half of the European population will have some type of allergy [3].

Allergy is a chronic disease

The prevalence of allergic disease is higher among young patients compared with older age groups [10]. This feature has incorrectly been interpreted as a sign of patients outgrowing their allergy. The Copenhagen Allergy Study is a repeated cross-sectional study of the general population [10]. Analyzing the same study group repeatedly showed an increase in prevalence of allergic disease in the younger age groups and no change in the older age groups, in agreement with a model in which the increase in prevalence began to gather pace at a certain time point around the 1960s [10,11]. Although some patients with allergy do experience a relative mitigation in symptoms with age, after eight years more than 85% were still symptomatic and 98% continuously had objective signs of allergic sensitization [12]. These data classify allergy as a chronic disease.

Allergy is a disease with many expressions

The most prevalent manifestation of allergy is respiratory allergic disease, a common designation for the related symptoms,

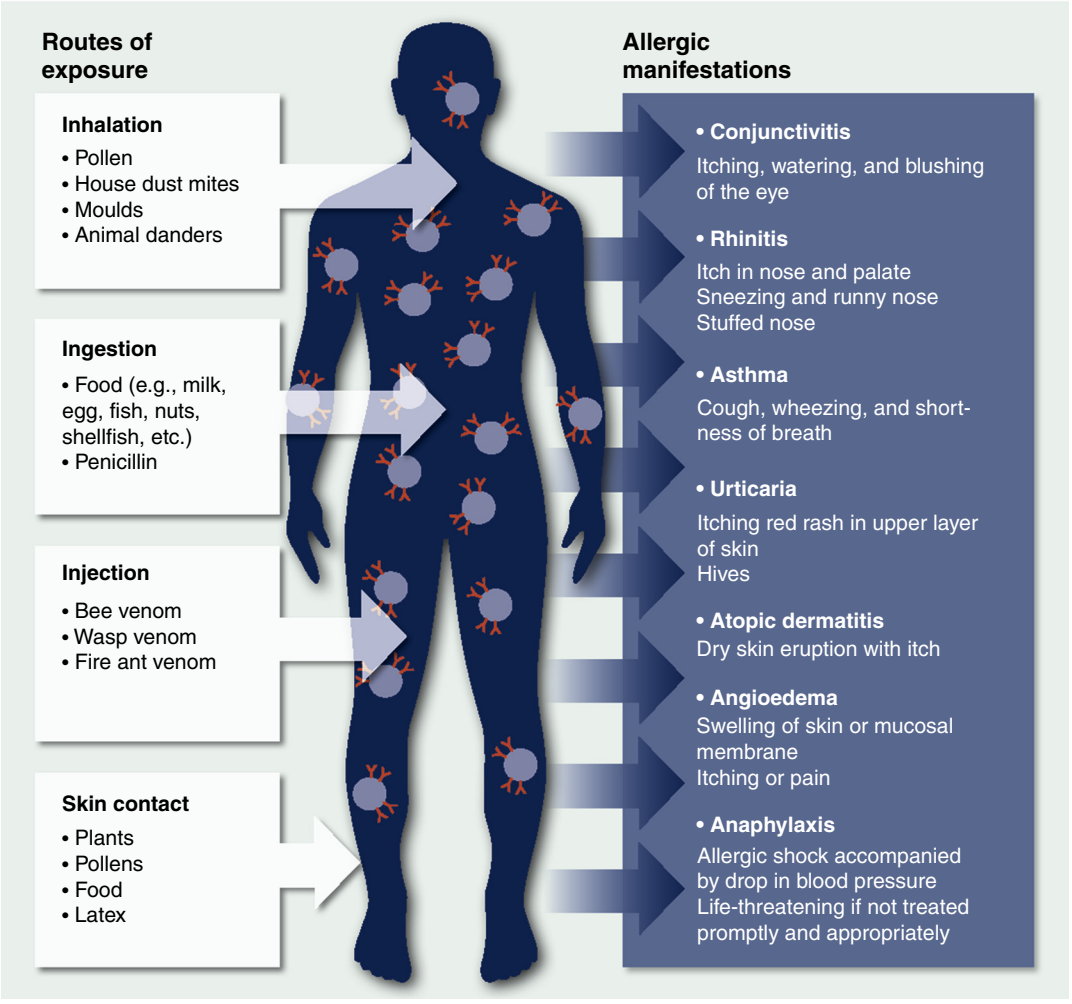

FIGURE 1

Allergy is a systemic disease in the immune system. Sensitization can occur following allergen exposure in the airways by inhalation, in the gastrointestinal tract by ingestion, in body fluids by insect sting or in the skin by physical contact. Regardless of the route of exposure, symptoms can manifest in one or more tissues; for example, in the eyes (conjunctivitis), nose (rhinitis), lungs (asthma), skin, either as a rash (urticaria), inflammation (atopic dermatitis), or swelling (angioedema), or in the whole body accompanied by a drop in blood pressure (anaphylaxis).

rhinoconjunctivitis (hay fever) and asthma [1]. Respiratory allergic disease is caused by inhalation of organic dust, which is airborne particles containing allergen molecules. The particles land on the moist surface of the airway mucosa and the allergen molecules are extracted and presented to the immune system. Allergen molecules can be encountered by other routes, such as with a food allergy or allergy to the venom of stinging insects, but the basic immunological mechanisms are the same. Typical symptoms can vary according to the route of exposure, but manifest either in the nose, eyes, lungs, skin or gastrointestinal tract. Most patients have symptoms from multiple organs simultaneously and the expression of allergic disease can change over time. These observations point to a model where allergy is a systemic priming of the immune system with subsequent dynamic manifestations of symptoms in multiple organs (Fig. 1).

'The Allergic March'

'The Allergic March' was a term coined to reflect the common progression of disease starting in infancy as eczema and food allergy [13,14]. By the age three years, many children experience spontaneous remission, but with increased risk of acquiring respiratory allergic disease later in childhood or adolescence [15]. Furthermore, children with rhinoconjunctivitis have a high risk of developing concomitant asthma. By the age of seven years, asthma is three times more common among children with allergic rhinoconjunctivitis compared with children without rhinoconjunctivitis [16]. All sensitized individuals are likely to develop new allergies. Thus, in the Copenhagen Allergy Study, the risk of developing new IgE sensitization during an eight-year period was three times higher among patients who were already sensitized compared with patients without previous sensitization, and the risk increased further with the number of allergies at baseline [17].

Allergy is a disease of the immune system

The hallmarks of allergic disease (i.e., specificity and memory) are profound features of the immune system, and recent consensus on disease mechanisms in allergy is concerned with cells and

mediators residing in the immune system [18]. Thus, allergy is a disease in the immune system and disease manifestations are not limited to specific organs over time, as reflected in the allergic march. For instance, most patients with allergic asthma also have rhinoconjunctivitis [19]. The causal relation between systemic sensitization and allergic symptoms from different organs received broad recognition when the WHO endorsed the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative [6].

Allergic symptoms are difficult to control with pharmacotherapy

Many patients with allergy receive treatment with pharmacotherapy, such as antihistamines and nasal corticosteroids for rhinoconjunctivitis [5] and bronchodilators and inhaled corticosteroids for asthma (http://www.ginasthma.org/). Such medication has been shown in controlled trials to be effective in reducing symptoms, but do not address the underlying allergy and do not prevent disease progression [20]. Furthermore, 57% of patients report troublesome symptoms and describe symptom control as being poor despite the fact that their symptomatic treatment is guided by a physician [21,22]. Sixty-nine percent of patients are restricted in their daily life [19]. These observations indicate that pharmacotherapy alone is insufficient to control symptoms in all patients.

Allergy is a severe disease in some patients

Disease severity refers to the reduced function of the organs induced by the disease process or to the occurrence of severe acute exacerbations [23]. Comorbidities add to the complexity of defining disease severity. The symptom severity of allergic disease varies from mild to severe and from intermittent to persistent, whereas exacerbations can occur in any patient regardless of severity [23]. Acute severe reactions include anaphylaxis, which is life threatening if not treated promptly and appropriately. Rhinoconjunctivitis can be classified using a simple system comprising four categories based on duration and symptom severity [5,6]. A French study found 11% of patients consulting a primary-care physician to have mild intermittent disease; 8% mild persistent; 35% moderate-to-severe intermittent; and 46% moderate-to-severe persistent [24]. The moderate-to-severe group of patients according to this classification was large and heterogeneous, and attempts to improve the usefulness of the classification for guidance of treatment are aiming to include measures of disease control [25]. Of those patients with rhinitis, 10–40% also have asthma [5].

Allergy significantly affects quality of life

Patients with allergy experience symptoms only when exposed to the offending allergen, but allergen exposure cannot be completely avoided. Many patients do not receive an allergen-specific diagnosis [19] and, therefore, patient education is not optimal. Patients with allergy try to adapt their behavior to avoid allergen exposure and symptoms, but this is a tedious process that is often not possible. Living with residual symptoms has a significant effect on allergic patients' quality of life, including physical functioning, energy, social functioning, general health perception, mental health, and pain [26]. Patients with allergy experience limitations in their daily life attributable to physical and emotional disturbances [26], and twice the number of patients with allergic rhinoconjunctivitis compared with controls, are affected by sleep disturbance [27]. Of patients with allergic rhinoconjunctivitis, 79% are impaired in their professional life [28].

Allergy is a significant burden to society

The burden of allergic disease to society is distinct in two aspects: first, patients with allergy use resources when utilizing the healthcare system. In pharma-economic terms, these costs are the direct costs, and include emergency room visits, visits to outpatient clinics, and medicinal costs [29]. A certain percentage of these patients have severe symptoms, representing a high cost in this category [30]. The second aspect is associated with reduced performance at work or in school, the so-called 'indirect costs' [31]. Patients in this category cause a large burden because of their high numbers [28] (http://www.theipcrg.org/display/TreatP/2012/03/28/New%3A+Respiratory+Allergies+book). Patients with moderate allergic disease might not take many sick days per year, but while present at work or school, they might still be affected by symptoms and have a suboptimal performance. As noted above, 79% of patients with allergic rhinoconjunctivitis are impaired in their professional life [28]. An American study showed allergic rhinitis to be the most costly disease of all, from an employer perspective [32].

Allergy immunotherapy

Background

The concept of allergy immunotherapy recently celebrated its 100-year anniversary, based on the first scientific publication, in *The Lancet*, by the British doctor Leonard Noon in 1911 [33]. Noon described observations by subcutaneous inoculation of a pollen extract into a few patients and, although allergen immunotherapy in principle is conducted in a similar way today, major progress has been made, in particular in three important areas: (i) the mechanistic understanding of the mode of action; (ii) the quality of vaccines; and (iii) the quality of clinical documentation.

Mechanistic mode of action

Allergy immunotherapy changes the response to allergen exposure by inducing immunological tolerance [34]. A patient with allergy has symptoms only when exposed to the relevant allergen. For respiratory allergies, allergens arrive at the airway mucosa airborne on particles present in the air breathed. Upon contact with the moist surface of the mucosa, the allergen molecules are extracted and come into contact with the immune system. Allergen is bound by allergen-specific IgE antibodies, which leads to activation of mast cells and basophils, and rapid release of histamine and other mediators directly responsible for allergic symptoms. In addition, allergen-specific T cells are activated, leading to an inflammatory reaction (Fig. 2). The blood vessels dilate and leak plasma and cells into the mucosal tissue. The inflammatory response activates mast cells, basophils, eosinophils, neutrophils, and macrophages, and attracts them to the airway mucosa, giving rise to bronchoconstriction and mucus secretion. Eyes redden and flood with tears and the nose sheds aqueous secretion. Itching in the nose, palate, throat, and eyes is characteristic of the allergic response and distinguishes allergic symptoms from those of infectious disease.

When allergen is taken up by natural exposure, the amount of allergen presented to the immune system in the mucosa is relatively low, but the result is efficient stimulation of the allergic

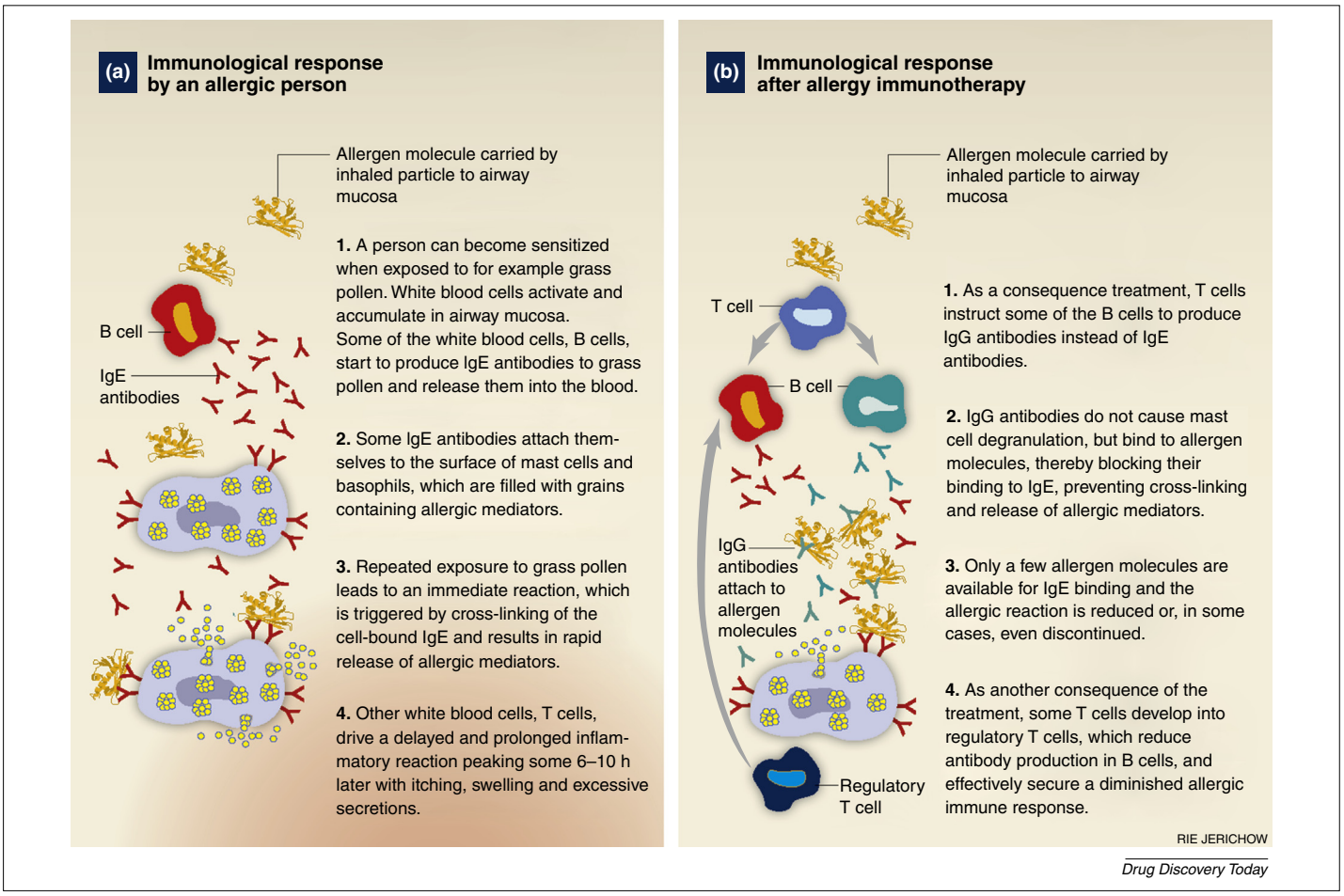

FIGURE 2

Immunological responses. **(a)** An allergic reaction is initiated when the immune system is unintentionally sensitized to a molecule that does not represent a threat to the body. The immune system reacts by developing antibodies [e.g., immunoglobulin E (IgE) antibodies] and T cells that are specifically reactive with the allergen molecules. The resulting interactions trigger allergic symptoms, such as allergic rhinitis and asthma. **(b)** The immunological response is modified by allergy immunotherapy inducing immunological tolerance through induction of IgE-blocking IgG antibodies and regulatory T cells. This treatment can result in no, fewer, or less severe allergic reactions.

response and symptoms will appear within minutes. By contrast, when allergen is administered as immunotherapy, the amount of allergen is relatively high. One dose administered in immunotherapy, either sublingually or subcutaneously, corresponds approximately to 100 times the estimated maximal yearly intake through natural exposure [35]. The quantitative difference in combination with the different route of entry into the body exerts a profound effect on the immune system, which responds by inducing immunological tolerance to the allergen. Two mechanisms are thought to have a major role: immune deviation and induction of regulatory T cells [36].

Immune deviation is a term signifying a modified immunological response to allergen exposure, where allergen-specific T helper type 1 (Th1) cells are mobilized and stimulated at the expense of Th2 cells. Th1 cells produce interferon gamma (IFN-γ), stimulating B cells to produce IgG instead of IgE, and IgG is not capable of triggering an allergic reaction.

Regulatory T cells are a diverse group of T cells that are active in the regulation of immune responses, and allergen-specific $CD4^+CD25^+$ regulatory T cells have been demonstrated after allergy immunotherapy [37]. They produce interleukin (IL)-10 and transforming growth factor (TGF)-β, and have the potential to suppress local Th2 cell responses and redirect antibody class switching in favor of IgG_4 (IL10 isotype switch factor), and IgA (TGF-β isotype switch factor) (Fig. 2). Allergen-specific IgG_4 antibodies interrupt allergen presentation to Th2 cells and, in addition, block allergen-induced activation of mast cells and basophils, thereby significantly weakening the allergic reaction.

The relative contributions from immune deviation and regulatory T cells are not established, but the end result is reduction and, in some cases, even elimination of the capacity to mount an allergic reaction in response to allergen exposure.

Treatment modalities

The original administration form of allergy immunotherapy was by subcutaneous injection (SCIT). This treatment regimen is traditionally conducted in two phases: an initial up-dosing phase and a subsequent maintenance phase. The up-dosing phase is an individual titration, where increasing doses are administered for the purpose of slowly building tolerance and carefully assessing the sensitivity of the patient. The maximum-tolerated dose, or the maximum dose recommended, whichever is reached first, is then

given throughout the maintenance phase. All injections are given in the doctor's surgery because there is a small risk of inducing allergic reactions, which can become severe or even life threatening if not treated promptly and appropriately.

In Europe, products for SCIT are typically formulated with aluminum hydroxide, which forms a complex with the active protein ingredient, acting as a depot and releasing the allergens slowly. Importantly, the allergen extract must be standardized to achieve a reproducible composition and thereby facilitate a predictable outcome of the treatment. The European allergen products are distributed with recommendations for use and packaged into treatment sets for individual patients. Only a few products are approved by regulatory authorities and most are sold as named patient products [38]. In the USA, allergen products for SCIT are sold as aqueous bulk extract, which is then mixed and diluted for the individual patient in the doctor's surgery, and administered as subcutaneous injections [7].

Other administration routes have been investigated, including all mucosal surfaces; the most frequently used is sublingual administration under the tongue. The treatment is given either as drops or fast-dissolving tablets. The majority of the market for drop products comprises named patient products, although sublingual immunotherapy has only limited distribution in the USA.

Fast-dissolving tablets for sublingual immunotherapy have recently been developed in comprehensive clinical trial programs and, as such, they must be considered the only marketed allergy immunotherapy products to meet current requirements for regulatory approval. Two European manufacturers (ALK, Denmark, and Stallergenes, France) have initiated strategies to develop SLIT tablets with the aim of authorization in major European markets and further propagation to more continents. At present, two products have received marketing authorizations in Europe and three in the USA, and, for all products, the treatment regimen is once-daily administration, with a safety profile that allows home use.

Quality of immunotherapy products

Allergen products are used for allergen-specific management of allergic disease. No structural feature defining an allergen has hitherto been described and the definition of an allergen is based solely upon the functional criterion of being able to elicit an IgE response in susceptible individuals. Thus, the allergen is defined by the immune system of the individual patient. Every patient has a unique sensitization pattern with respect to molecules and epitopes. Based on this definition, any immunogenic protein (antigen) has allergenic potential, even though most patients with allergy have IgE antibodies specific for a relatively limited number of 'major' allergens.

All marketed allergen products are manufactured by aqueous extraction of allergenic source materials derived from natural raw materials, such as pollens, house dust mite cultures, animal hair and/or dander, or insect venoms. Natural raw materials are inherently variable in composition and, therefore, standardization is of major importance [39,40]. The standardization procedure includes all aspects of the manufacturing procedure, from selection and collection of raw materials, securing collector qualifications, extract preparation and storage, to validation of assays and reagents [41].

Control of the variation in the natural source material is handled by use of references and control extracts. In Europe, each manufacturer establishes their own in-house reference preparations (IHRP), which must be matched by each and every batch. New batches are compared with the IHRP using a combination of laboratory techniques to achieve a uniform composition with regard to complexity of the extract, the content of major allergen, and the IgE-binding potency. In the USA, the US Food and Drug Administration (FDA) issues standards and assays to be used by all manufacturers.

Different manufacturers use different raw materials, production processes, and standardization procedures, and, therefore, allergen products are not generic, but differ in their composition, IgE-binding potency, and extent of quality control between manufacturers. No international standards are in effect. This means that products from different manufacturers can perform differently in patients and, as a consequence, clinical results cannot be extrapolated directly from one allergen product to another [42].

Currently, different immunotherapy products with different qualities of clinical documentation are available on the market for the treatment of the same allergy. In such cases, selection of an authorized product with the highest level of evidence would optimize safety, efficacy, reproducibility, and, hence, predictability of the treatment. Once a patient has been identified as eligible for immunotherapy, the choice of either subcutaneous or sublingual immunotherapy might rely on more practical patient preferences.

Clinical documentation

Since the first report of allergy immunotherapy appeared in the literature some 100 years ago [33], many studies have reported the efficacy of allergy immunotherapy in different allergies, seasonal as well as perennial, and different indications, rhinoconjunctivitis as well as asthma. However, many published trials are small and the documentation is heterogeneous with respect to indications and design. Some early trials were planned with an element of exploration and they do not fulfill the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) criteria for a therapeutic confirmatory trial (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf). In addition, products for allergy immunotherapy are not generic, as discussed above, and results from trials with different products cannot be taken as a demonstration of a class effect as such. For these reasons, the interpretation of the clinical documentation for allergen immunotherapy requires caution [43].

More recently, SLIT tablets have been documented in comprehensive clinical development programs designed to fulfill regulatory requirements for market authorization and, currently, SLIT tablets are the best-documented immunotherapy products.

Recent guidelines include recommendations for the treatment of allergic rhinitis in concordance with the grades of recommendation, assessment, development, and evaluation principle focusing more critically on clinical relevance and cost effectiveness [44]. To advance the quality of documentation, the European Medicines Agency (EMA) has published guidelines for product registration regarding production and quality issues

(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003333.pdf), and for the clinical development of immunotherapy products (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003607.pdf). Furthermore, the *Monograph on Allergen Products in the European Pharmacopoeia* was recently updated [45].

Subcutaneous immunotherapy

The WHO Position Paper on Immunotherapy [46] made recommendations regarding composition and dosing for products intended to be used for SCIT. Analysis of the published clinical data through the Cochrane Collaboration provided scientific evaluation and expanded the evidence base for subcutaneous immunotherapy for both rhinoconjunctivitis [47] and asthma [48]. The ARIA document [5], under the auspices of the WHO, assigned allergy immunotherapy the highest level of evidence (i.e., level Ia). As mentioned above, the heterogeneity in the included studies was substantial and potential publication bias could not be excluded. One large trial has been performed in adult patients with grass pollen-induced allergic rhinitis. Patients had moderately severe symptoms that were inadequately controlled with standard pharmacotherapy and the study demonstrated reductions in symptom and medication use as well as improvement in quality of life after one season of SCIT [49].

SLIT drops

Meta-analysis of grass pollen immunotherapy trials [50] show that published SLIT-drop trials show greater heterogeneity compared with SCIT trials, suggesting that some SLIT-drop products have efficacy similar to SCIT, whereas others do not. The efficacy of SLIT in general has been demonstrated in four meta-analyses for allergic rhinoconjunctivitis and four meta-analyses for asthma, including both children and adults [43]. One Cochrane review analyzed the results and documented efficacy of SLIT drops in seasonal and perennial rhinitis in both children and adults [51]. The ARIA document [5] also assigned sublingual immunotherapy the highest level of evidence, although, as mentioned above, the heterogeneity in the included studies was substantial and each product has to be evaluated separately by available data. One large trial has been performed in adult patients with ragweed pollen-induced allergic rhinoconjunctivitis; the study demonstrated reductions in total combined symptom and medication scores [52].

SLIT tablets

SLIT tablets have been developed in comprehensive clinical development programs designed to meet regulatory requirements for marketing authorization in Europe. Currently, SLIT tablets are the best-documented immunotherapy products on the market, and the only products that are developed to meet current standards for clinical documentation in both the USA and Europe. The studies are large, randomized, double-blinded, controlled and confirmatory [43]. In parallel and partly because of the emergence of these large studies, new European guidelines have been established (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003607.pdf). So far, 14 large studies based on SLIT tablets have been published (Table 1).

TABLE 1

The large SLIT-tablet immunotherapy studies

Characteristic of study	Treatment	Clinical trial identifier	Refs
Grass pollen allergy			
Phase II	Grazax	n.a., GT02	[56]
	Oralair	NCT00367640, VO34.04	[77]
Phase III	Grazax	NCT00227279, GT08	[74,80,95]
	Oralair	NCT00418379, VO53.06	[58]
Disease modification	Grazax	NCT00227279, GT08	[57]
USA	Grastek	NCT00421655, GT14	[96]
	Grastek	NCT00562159, P05238	[81]
	Oralair	NCT00955825, VO61.08	[82]
Children	Grazax	NCT00408616, GT12	[78]
	Grastek	NCT00550550, P05239	[83]
	Oralair	NCT00409409, VO52.06	[79,97]
Ragweed pollen allergy			
USA	Ragwitek	NCT00783198, P05233	[84]
	Ragwitek	NCT00770315, P05234	[85]
House dust mite allergy			
	Under development	NCT00674700, VO57.07	[98]
	Under development	NCT00389363, MT02	[99,100]

Note: GRAZAX® is the registered trade name for the SQ-grass SLIT tablet in Europe. GRASTEK® is the registered trade name for the SQ-grass SLIT tablet in the USA. ORALAIR® is the registered trade name for the 5-grass SLIT-tablet.

Allergy immunotherapy improves quality of life

Allergy is peculiar in that the burden of disease varies considerably between times of exposure versus nonexposure to allergens. The quality of life of patients with allergy deteriorates during exposure to the relevant allergen; however, immunotherapy diminishes the reduction and thereby improves quality of life for these patients.

There is no consensus on how patient-reported outcomes should be calculated and there is no validated standard for reporting health impact for allergy immunotherapy. Most often used is the disease-specific Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) developed to assess seven domains of the quality of life in symptomatic patients during allergen exposure (e.g., during a pollen season), allowing for assessment of a symptomatic baseline [53]. A minimal important difference for change in the actively treated group of 0.5 has been proposed based on studies of pharmacotherapy [54]; however, in clinical trials of seasonal allergen immunotherapy, subjects are typically randomized during a preseasonal, relatively asymptomatic period, and results reflect the difference between groups treated with active treatment versus placebo. Evaluating symptoms in a previous season will not lead to valid baseline values, because symptoms are dependent on exposure, which varies from year to year [55]; however, baseline assessment might be relevant for perennial allergies, such as allergy to house dust mites. A minimal important difference appropriate to the design of clinical trials of allergy immunotherapy, without a symptomatic baseline and comparing treatment groups rather than change from baseline, has not yet been established.

Three large trials of SLIT tablets demonstrated a statistically significant improvement in quality of life among patients with grass pollen allergic rhinoconjunctivitis during the pollen season [56–58]. All studies used the disease-specific RQLQ instrument [53]. In the long-term trial with the SQ grass SLIT tablet, the highest effects were observed in the sleep and eye symptom domains [59]. Impaired sleep exerts a particular effect on patients' well-being, as well as school and work performance, and, therefore, has a major impact on quality of life. The beneficial effect of immunotherapy was sustained for two years after the

end of treatment [57]. A large study also demonstrated significant improvement in quality of life using subcutaneous injection immunotherapy [60]. All domain scores improved significantly using the RQLQ instrument [53].

Allergy immunotherapy is cost effective

The societal cost of allergic disease is considerable, mainly because of the high prevalence of allergic rhinoconjunctivitis and the associated loss of productivity. A Swedish study estimated the cost of lost productivity caused by rhinitis at EUR 2.7 billion per year in Sweden [31], and an American study established rhinitis as the most costly disease for American employers [32]. Allergy immunotherapy implies treatment over at least a three-year period, but as the objective of the treatment is induction of immunological tolerance, the effect might persist several years thereafter. This aspect of disease modification has been demonstrated clinically for only a few products [57,61]. Where such data are available, the total healthcare cost of the treatment could be regarded as an investment, with returns in the form of cost savings over the following years because of disease modification [62–64].

Theoretically, the societal benefit of allergen immunotherapy is associated with cost savings caused by decreased consumption of pharmacological products, fewer visits to general practitioners and specialists, as well as incurred productivity gains. In addition, disease modification potentially leads to a reduced risk of developing asthma [65], which is of societal benefit because of the costs associated with the more severe disease in patients with asthma patients (http://www.theipcrg.org/display/TreatP/2012/03/28/New%3A+Respiratory+Allergies+book).

Both SCIT and SLIT tablets are cost effective [66], with the latter being so in both Northern [67] and Southern [68] European countries.

State-of-the-art

Allergy immunotherapy tablets

As mentioned previously, fast-dissolving allergen immunotherapy tablets for sublingual administration have been, and are currently being, developed by the industry in comprehensive clinical development programs designed to satisfy current requirements for market authorization. The clinical development programs comprise Phase I safety and tolerability studies, large Phase II dose-finding studies, and large Phase III efficacy and safety studies, including studies in patients with rhinoconjunctivitis as well as asthma, and studies in adults as well as in children. All studies are randomized, double blinded and placebo controlled, and all patients enrolled have free access to standardized rescue medication. The primary outcome of SLIT-tablet trials is based on symptom and rescue medication scores recorded daily.

Currently, three products have been developed in accordance with applicable regulatory requirements for marketing authorization. The SQ grass SLIT tablet (ALK, Denmark) and a ragweed SLIT tablet in the same formulation, and the 5-grass SLIT tablet (Stallergenes, France). The SQ grass SLIT tablet is a fast-dissolving tablet of a freeze-dried formulation containing grass pollen extract from one grass species, *Phleum pratense* [69], whereas the 5-grass SLIT tablet is a multiparticulate tablet produced by compression and containing a mixture of pollen from five homologous grass species with high IgE cross-reactivity [70].

For the SQ grass SLIT tablet, simultaneous authorization in 27 European countries was based on Phase I–III studies comprising almost 1800 patients [56,71–75]. A large dose-finding trial ($N = 855$ patients) established the optimal dose [56], which was then documented in a large safety and efficacy study ($N = 634$ patients) [57]. For the 5-grass SLIT tablet, the clinical development program comprised Phase I, II, and III studies, including 1350 patients [58,76,77]. A large dose-finding trial ($N = 628$ patients) established the optimal dose, which was then documented in a large safety and efficacy study ($N = 633$ patients) (Table 1).

During pre- and co-seasonal treatment for one grass pollen season, similar clinical results were obtained with the SQ grass SLIT tablet and the 5-grass SLIT tablet [56,77]. Likewise, similar results were obtained in children for treatment in one season with the two products [78,79] and for adults treated for three seasons [58,80]. Studies performed in Europe [56,77] yielded results similar to those obtained in North America [81,82] for adults, and also for pediatric patients using the SQ grass SLIT tablet [78,83] (Table 1).

A SLIT tablet for the treatment of ragweed pollen allergy has also been developed. Two large randomized, double-blinded placebo-controlled trials have been published demonstrating clinical efficacy in adult patients with ragweed pollen-induced rhinitis with or without conjunctivitis [84,85].

The safety profile of the SLIT tablets support at-home use once the first dose is tolerated when administered under physician supervision. This procedure allows for not only possible treatment of any immediate adverse effects in sensitive patients, but also discussion of local adverse effects, such as mild itching and mild swelling of the lips and floor of the mouth, which are common but usually of short duration and, in most patients, cease to occur after a few weeks of treatment.

Disease modification: post-treatment effect

The capacity of allergy immunotherapy to modify the natural course of allergic disease was first discussed in by Noon in 1911. He noted that patients who developed 'active immunity' against the pollen toxin became 'cured' of their rhinoconjunctivitis symptoms. The long-term trial with the SQ grass SLIT tablet comprised three years of daily treatment and a two-year follow-up period to demonstrate disease modification through post-treatment effects [57] (Fig. 3). There was a significant reduction in symptoms compared with placebo during the treatment period, and this reduction was maintained during follow-up; thus, the indication 'disease-modifying treatment' was approved by the European authorities. The SQ grass SLIT tablet is the only immunotherapy tablet so far with this approved indication.

The long-term confirmatory trial with the 5-grass SLIT tablet comprised three years of pre- and co-seasonal treatment followed by a two-year follow-up period to demonstrate disease modification through post-treatment effect (ClinicalTrials.gov identifier: NCT00418379) [86,87]. Although there was a statistical significant difference between active and placebo at all time points [88,89], 'disease modification' is not in the label of this product.

Disease modification: prevention

Another element of disease modification is prevention, and preventive effects of allergy immunotherapy might be possible on

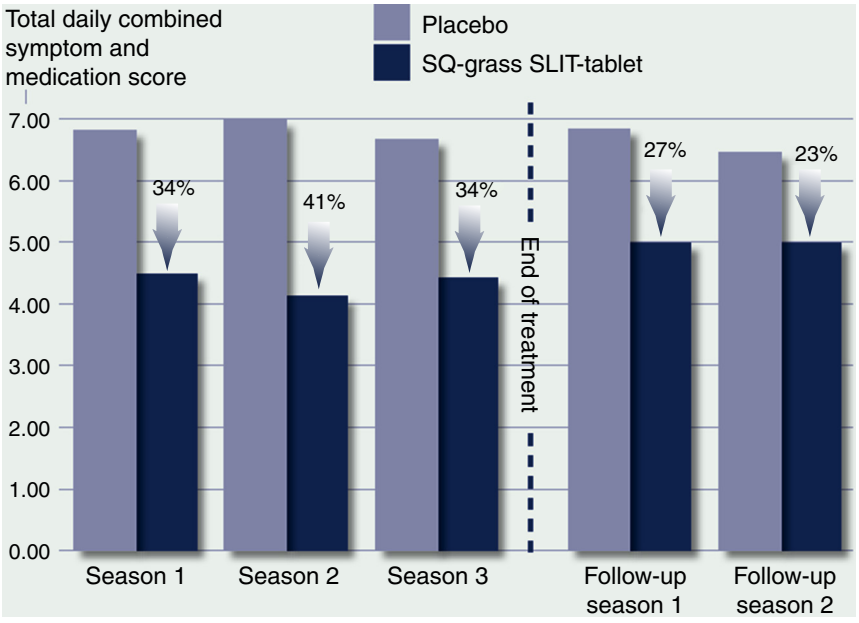

FIGURE 3

Long-term effect of the SQ grass SLIT-tablet showing a sustained effect of allergy immunotherapy two years after termination of three years of daily treatment using a fast-dissolving tablet under the tongue. The tablet contained a standardized grass pollen extract in a freeze-dried formulation. All patients in the study had access to standard pharmacotherapy as needed.

several levels. The WHO report on *Prevention of Allergy and Allergic Asthma* (http://whqlibdoc.who.int/hq/2003/who_nmh_mnc_cra_03.2.pdf) defines primary prevention as prevention of immunological sensitization (i.e., the development of IgE antibodies). Secondary prevention is defined as preventing the development of disease in sensitized individuals, especially preventing the development of atopic eczema, rhinoconjunctivitis, and allergic asthma. Tertiary prevention is defined as preventing an attack of illness in patients with asthma and/or allergic diseases.

However, this definition does not take into account that immunotherapy might provide different types of secondary prevention. For example, preventing asthma in children with rhinoconjunctivitis can also be considered secondary prevention, and this is also true for the prevention of new sensitizations in individuals who are already sensitized to one allergen.

Furthermore, preventing attack of illness in patients with asthma and/or allergic disease is referred to as tertiary prevention in the WHO definition (http://whqlibdoc.who.int/hq/2003/who_nmh_mnc_cra_03.2.pdf). However, whether this is at all prevention or merely corresponds to a symptom-relieving and/or controlling effect during treatment is unclear. For these reasons, we consider the current terminology to be insufficient, and propose a more specific and comprehensive terminology concerning prevention, as outlined in Table 2.

The natural history of allergic disease starts with family disposition or genetic susceptibility. Genetic susceptibility is an inherited predisposition to become allergic. However, before disease can manifest, the immune system must be primed, an event referred to as sensitization. During sensitization, the immune system is primed for a specific allergic reaction, and cells and molecules

TABLE 2

Proposed new prevention terminology[a,b]

	Type of effect	Effect during ongoing treatment	Post-treatment effect
Primary prevention	Prevention of first sensitization	×	×
Secondary prevention	Prevention of clinical symptoms in sensitized individuals	××	××
	Prevention of new sensitizations with clinical manifestations; e.g., birch pollen allergy in patients with grass pollen allergy	××	××
	Prevention of progression to new clinical manifestations; e.g., asthma in patients with rhinoconjunctivitis	××	××
Treatment	Improve control of symptoms	0	××

[a] Allergy is a systemic disease of the immune system characterized by sensitization and the occurrence of allergen specific IgE. From this initial asymptomatic state, disease can propagate and, consequently, all the preventive effects mentioned above are examples of disease modification. According to this definition, the prevention of first clinical symptoms in sensitized individuals is also secondary prevention, although in practical terms this is normally considered to be disease prophylaxis.

[b] ×, disease prophylaxis; ××, disease modification; 0, symptom relieving and/or controlling during treatment.

necessary for the organization of an allergic attack are formed and immunological memory is stored. In this sequence of events, two levels of prevention are theoretically possible, that is, prevention of sensitization in healthy individuals, and prevention of disease in sensitized individuals.

Prevention of first sensitization (i.e., prevention of sensitization in healthy individuals) is primary prevention, whereas preventing clinically manifest disease in individuals with sensitization is secondary prevention (Table 2). Both these levels of prevention can be considered disease prophylaxis because allergic symptoms have not yet occurred, although a preclinical disease state has been initiated.

Having established sensitization with disease implies a high risk of disease progression in two dimensions. First, one disease might develop into two clinical manifestations (e.g. rhinoconjunctivitis caused by a specific allergen might develop into rhinoconjunctivitis with asthma caused by the same allergen). Second, one allergy (e.g., to house dust mites) might develop into two allergies (e.g., to house dust mites and grass pollen). According to our proposed terminology, secondary prevention is further separated into prevention of progression to new clinical manifestations, and prevention of development of additional sensitizations and/or allergies.

All these preventive effects can theoretically be characterized as effects occurring during ongoing treatment or they can be post-treatment effects when treatment has been terminated. Disease modification also includes post-treatment control of symptoms, because the immunological modification resulting from allergy immunotherapy has resulted in a sustained reduction in the response to allergen exposure.

Ongoing prevention studies

Studies of primary prevention are currently in progress. This is prevention of the first allergic sensitization, and children are consequently selected on the basis of family history, because allergy among parents and/or siblings is a strong predictor of allergy later in life. In the Mite Allergy Prevention Study (MAPS) [90], 120 children five to six months of age at high risk of developing allergy were treated with SLIT drops containing house dust mite allergen extract twice daily for one year. The children are being assessed regularly at three-month intervals for the appearance of allergic sensitization by skin prick test. Given that asthma is difficult to diagnose precisely at this age, a follow-up at five years of age is planned to assess asthma development.

Another study, which preceded the MAPS study and showed good tolerability, was the Global Prevention of Asthma in Children (GPAC) study. However, the study was terminated after the pilot phase [91], because no difference in treatment-allergen specific IgE/IgG antibodies or associated Th cell responses could be detected between active and placebo groups at six months of treatment. The reason why this requirement to proceed beyond the pilot phase was included in the protocol was that infants could not be trained to hold the liquid under the tongue for two minutes, and thus there was a risk that the amount of allergen penetrating through the mucosa would be under the threshold required for triggering immunologic processes.

A few studies have looked at secondary prevention in the form of asthma prevention in children with rhinoconjunctivitis.

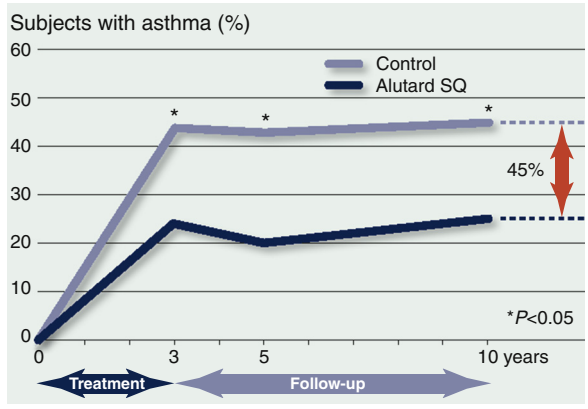

FIGURE 4

Prevention of the development of asthma in children with allergic rhinoconjunctivitis after three years of subcutaneous injection immunotherapy. Only approximately half as many children in the immunotherapy-treated group developed asthma compared with the control group. Both groups of children had access to standard pharmacotherapy as required.

One randomized and controlled open trial was the PAT-trial, where children with allergic rhinoconjunctivitis were followed for ten years with asthma development as the primary outcome [65] (Fig. 4). The children in the active group were initially treated with immunotherapy for three years, and asthma incidence was recorded at three, five, and ten years after initiation of treatment. The intervention group showed a significant positive odds ratio for reducing the risk for development of asthma at the end of treatment after three years compared with the control group. The difference was maintained at follow-up after ten years.

A large ongoing asthma prevention trial, the (GAP) trial, is designed to assess the preventive effect of the SQ grass SLIT tablet on the development of asthma in children with allergic rhinoconjunctivitis in a trial designed to comply with current regulatory standards. In total, 812 children were enrolled in a randomized, double-blinded, placebo-controlled multicenter study comprising 101 sites in 11 European countries [92]. The trial is designed with three years of treatment and two years of follow-up.

Prevention of new sensitizations in sensitized individuals has been reported in a few small studies [93], but data are currently not available from large randomized, controlled studies.

Concluding remarks

The number of patients with allergies is on the increase worldwide, and it appears that current healthcare measures to control this disease are inadequate. The European Federation of Allergy and Airways Diseases Patients' Associations, EFA, has issued a call for action to raise awareness and improve treatment of respiratory allergy (http://www.theipcrg.org/display/TreatP/2012/03/28/New%3A+Respiratory+Allergies+book). One of the action points specifically highlights the unique property of allergy immunotherapy to modify the course of respiratory allergy and requests the European Union and Member States to improve access to preventive and/or disease-modifying treatments. In addition,

the European Academy of Allergy and Clinical Immunology has issued a European Declaration on Immunotherapy focusing on allergy immunotherapy as the foundation for the battle against allergy, a public health threat of pandemic proportions [3].

The unique aspect of allergy immunotherapy is the capacity to modify the natural course of disease by inducing long-term immunological tolerance; therefore, future directions for immunotherapy should be concerned with providing evidence of the different levels of disease-modifying effects, *cf*. Table 2.

Conflict of interest

All authors are employed by ALK A/S (http://www.alk.net), a private company engaged in the manufacturing, distribution and marketing of vaccines for allergy immunotherapy.

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